DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Marc S. Ayers
Manager and Chief Executive Officer
Romark Laboratories, L.C.
3000 Bayport Drive, Suite 200
Tampa, FL 33607

RE: NDA #s 21-497, 21-498, 21-818
Alinia® (nitazoxanide) Tablets and (nitazoxanide) for Oral Suspension
MACMIS ID # 17360

WARNING LETTER

Dear Mr. Ayers:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a sales aid (AL-SAGI-0708) for Alinia® (nitazoxanide) Tablets and for Oral Suspension (Alinia) disseminated by Romark Laboratories, L.C. (Romark) at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the Infectious Diseases Society of America 46th Annual Meeting (ICAAC/IDSA) held in Washington DC. DDMAC has also become aware of oral statements made about the drug by Romark sales representatives at the same conference. The sales aid and oral statements are false or misleading because they promote unapproved uses and broaden the indication for Alinia, make unsubstantiated superiority claims, omit and minimize the risks associated with Alinia, and/or make misleading compliance claims. Thus, these promotional activities and materials misbrand Alinia in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a); (f)(1); (n) & 321(n), and FDA implementing regulations. *See* 21 CFR 201.100(c)(1); 201.128; 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (ii). In addition, Romark failed to submit the sales aid to FDA under cover of Form FDA-2253, as required by 21 CFR 314.81(b)(3)(i). These violations are a concern from a public health perspective because they suggest that the product is safer and more effective than has been demonstrated.

Background

According to the INDICATIONS AND USAGE section of the approved product labeling (PI) for Alinia (in pertinent part):

> Alinia for Oral Suspension (patients 1 year of age and older) and Alinia Tablets (patients 12 years and older) are indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*.

> Alina for Oral Suspension and Alinia Tablets have not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients . . . .

The PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the PI state that Alinia has ". . . not been studied for the treatment of diarrhea caused by *Giardia lamblia* in HIV-infected or immunodeficient patients. [Alinia has] not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients."

The CLINICAL STUDIES section of the PI reports that "[a] double-blind, placebo-controlled study did not produce clinical cure rates that were significantly different from the placebo control when conducted in hospitalized, severely malnourished pediatric patients with acquired immune deficiency syndrome (AIDS) in Zambia."

With regard to dosing, the DOSAGE AND ADMINISTRATION section of the PI describes that the age-based dosing of Alinia is given for a duration of 3 days.

Additionally, the PI contains the following safety information (in pertinent part, emphasis in original):

> **PRECAUTIONS**
> **General**: The pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function have not been studied. Therefore, nitazoxanide must be administered with caution to patients with hepatic and biliary disease, to patients with renal disease and to patients with combined renal and hepatic disease.
> . . .
>
> **Drug Interactions**
> Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur (e.g., warfarin).

Promotion of Unapproved Uses/Broadening of Indication

Oral Statements

On October 26 and 27, 2008, during the ICAAC/IDSA conference, your representatives made the following claims:

- Alinia is effective for the treatment of diarrhea due to viruses, including rotavirus and enterovirus;
- Alinia is effective for the treatment of *Clostridium difficile*-associated diarrhea (CDAD); and
- Alinia is effective for the treatment of HIV/immunocompromised patients and is used in these patients for a duration of 7, 10, or 14 days.

Regarding the first two claims, according to the PI, Alinia is approved for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*, which are protozoa. Alinia is **not** approved for the treatment of diarrhea due to any virus, including rotavirus and enterovirus, or any bacteria, including *Clostridium difficile*. Regarding the third claim, the INDICATIONS AND USAGE section of the PI specifically states that Alinia has ". . . **not** been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients . . ." (emphasis added). (b) (4) Furthermore, according to the PRECAUTIONS section of the PI, Alinia has not been studied for the treatment of *Giardia lamblia* in HIV-infected or immunodeficient patients. Finally, with regard to dosing, Alinia is only approved for use for 3 days, not 7, 10, or 14 days.

Overall, the oral statements made by your representatives misleadingly suggest new "intended uses" for Alinia. Because the PI for Alinia lacks adequate directions for such uses, the drug is therefore misbranded.

Sales Aid

The sales aid is similarly misleading because it suggests that Alinia is approved in a broader range of conditions or patients than is reflected in the drug's PI.

Side one of the sales aid claims that Alinia is "**THE CHOICE FOR DIFFICULT-TO-TREAT GI** [GASTROINTESTINAL] **PATHOGENS**" (emphasis in original). This claim is followed by:

- the prominent header, "**Gastroenteritis: Differential Diagnosis**" (emphasis in original, footnote omitted);
- a list of "**Associated Symptoms**" (emphasis in original) consisting of diarrhea, nausea, vomiting, abdominal pain, fever, and weight loss; and
- a list of "**Potential Etiology**" (emphasis in original) of gastroenteritis, consisting of protozoal, viral, and bacterial.

This presentation is misleading for multiple reasons. First, this presentation is misleading because it suggests that Alinia is approved to treat **all** of the listed "associated symptoms" of gastroenteritis, when this is not the case. Alinia is **only** approved to treat diarrhea, which is one symptom of gastroenteritis. Second, this presentation suggests that Alinia is approved to treat gastroenteritis caused by protozoal, viral, and bacterial pathogens, when this is not the case. As stated above, Alinia is **only** approved for the treatment of diarrhea due to two specific protozoa, *Giardia lamblia* or *Cryptosporidium parvum*. The claim that Alinia is the choice for "**DIFFICULT-TO-TREAT**" GI pathogens further implies that the drug is effective against a wider range of pathogens than has been demonstrated by substantial evidence or substantial clinical experience. In immunocompetent patients, *Giardia lamblia* and *Cryptosporidium parvum* are not considered "difficult-to-treat" GI pathogens. On the contrary, these protozoa cause relatively mild, self-limiting disease in the population for which Alinia is indicated. Therefore, the claim misleadingly suggests that Alinia is effective for pathogens other than those for which it is approved.

We note that the approved indication and limitations regarding efficacy in HIV-infected or immunodeficient patients for Alinia are presented in the middle, right-hand side of the first side of the sales aid. However, this information is written in unbolded, extremely small font size in single-spaced paragraph format, making the information very difficult to read. In contrast, the surrounding claims are presented very prominently, written in bolded, large, colorful font, surrounded by a significant amount of white space and colorful, prominent graphics, as are the claims on the other side of the sales aid. These other claims and graphics can be easily seen by readers of the sales aid and draw attention away from the indication and precaution. Therefore, this presentation of the approved indication and precaution regarding HIV-infected or immunodeficient patients is not sufficient to mitigate the misleading impression created by the totality of the other presentations in the piece that Alinia is approved in a broader range of conditions or patients than is reflected in the drug's PI.

The second side of the sales aid also claims that Alinia is "**THE CHOICE FOR DIFFICULT-TO-TREAT GI PATHOGENS**." This claim is followed by the prominent header, "**A Safe Alternative to Metronidazole**" (emphasis in original), and a table comparing the dosing and risks of Alinia to Flagyl® (metronidazole) (Flagyl). This presentation implies that Alinia is a safe and effective alternative for the treatment of all of the GI diseases and causative pathogens for which Flagyl has been approved, when this is not the case. Alinia is not approved for **any** of the GI-approved uses of Flagyl.[1]

The second side of the sales aid also includes a table comparing the dosing of Alinia to Xifaxan® (rifaximin) (Xifaxan). This comparison table, in conjunction with the prominent header that Alinia is "**THE CHOICE FOR DIFFICULT-TO-TREAT GI PATHOGENS**", implies that Alinia is a safe and effective alternative for the treatment of the GI disease and causative pathogen for which Xifaxan has been approved, when this is not the case. Alinia is **not** approved for the same approved use as Xifaxan, which is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of the bacterium *Escherichia coli*.[2] We note the following information presented in small unbolded font beneath the table:

> Presented solely for the purpose of comparing FDA approved dosing of two 3-day GI anti-infective drugs. . . . Xifaxan® tablets are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli.* Please refer to the opposite side of this document for a summary of Alinia® indications.

However, this information does not mitigate the misleading impression created by the piece as a whole that Alinia is an approved alternative to Xifaxan.

In summary, the overwhelming impression created by these misleading presentations in the sales aid creates unapproved new uses and broadens the indication for Alinia.

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[1] See Flagyl PI, at http://www.fda.gov/cder/foi/label/2004/12623slr059_flagyl_lbl.pdf (Mar. 17, 2004).
[2] See Xifaxan PI, at http://www.fda.gov/cder/foi/label/2007/021361s006lbl.pdf (Jan. 30, 2007).

Unsubstantiated Superiority Claims

The sales aid and oral statements are misleading because they contain drug comparisons that represent or suggest that Alinia is safer or more effective than Flagyl and/or Xifaxan, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Sales Aid

The sales aid claims that Alinia is "**THE CHOICE**" for difficult-to-treat GI pathogens, followed by the header that Alinia is "**A Safe Alternative to Metronidazole**" (emphasis in original), and a table that compares the drug interactions, warnings, alcohol interaction, contraindications, and risk of neuropathy of the two drugs. This presentation misleadingly suggests that Alinia has a superior safety profile compared to Flagyl, when this is not supported by substantial evidence or substantial clinical experience. FDA is not aware of any adequate and well controlled, head to head clinical trials designed to compare the safety of these two products or of any substantial clinical experience to support this claim. Additionally, as discussed previously, the two drugs are not approved for the same indications and therefore comparison of their safety profiles is misleading.

The sales aid also contains misleading compliance comparisons. The sales aid includes a table that compares the dosing of Alinia (BID, or twice per day) to that of Flagyl (TID, or three times per day). It then claims that "Compliance with BID regimens (70%) is superior to TID regimens (52%)." The sales aid further compares the number of tablets of Alinia taken per day (2) to the number of Xifaxan tablets taken per day (3 based on the daily FDA approved dose, 3.9 based on prescription audit data). This presentation, in combination with the claim that Alinia is "**THE CHOICE**" for difficult-to-treat GI pathogens, implies that Alinia is superior to Flagyl and Xifaxan because it is associated with greater compliance than Flagyl and Xifaxan. The reference cited in support of the claim, "Compliance with BID regimens (70%) is superior to TID regimens (52%)", does not describe any head-to-head data comparing compliance with Alinia to compliance with Flagyl or Xifaxan.[3] Instead, it describes a study that determined compliance rates for BID and TID regimens based on a literature review of articles that examined compliance. The studies reported in these articles assessed compliance with many different classes of medications for a wide variety of diagnoses, including antibiotics, antacids, heart failure drugs, drugs for psychiatric or neurological disorders, and asthma drugs, and for a wide range of durations. Furthermore, the definitions of compliance and the methods used to measure compliance varied significantly from study to study. Therefore, this article does not constitute substantial evidence to support the representation conveyed by the sales aid that compliance with Alinia is greater than compliance with Flagyl or Xifaxan.

Oral Statements

Furthermore, your representatives claimed during the ICAAC/IDSA conference that Alinia is safer and more effective than metronidazole for the treatment of CDAD. However, as previously discussed, Alinia is not approved for CDAD, and it is therefore misleading to

[3] Greenberg RN. Overview of Patient Compliance with Medication Dosing: A Literature Review. Clinical Therapeutics. 1984;6(5):592-599.

suggest that Alinia is the better choice for this unapproved use. We are also not aware of any data to support the suggestion that Alinia is more effective than metronidazole for the treatment of CDAD.

Omission and Minimization of Risk Information

Sales Aid

The sales aid is false or misleading because it fails to reveal facts that are material in light of the representations made or with respect to the consequences that may result from the use of the drug as recommended or suggested in the piece.

Specifically, the sales aid claims that Alinia is "**A Safe Alternative to Metronidazole**" (bolded emphasis in original, underlined emphasis added), and that Alinia has "**Proven Safety, [and] Tolerability** . . . ." (emphasis in original). The sales aid also contains presentations listing risks that Alinia does **not** have in the table comparing Alinia to Flagyl. The table makes the following representations regarding Alinia:

- Drug Interactions – No significant inhibitory effect on cytochrome P450 enzymes;
- Warnings – No;
- Alcohol Interaction – No;
- Contraindications – No (footnote omitted); and
- Neuropathies – No.

This presentation clearly implies that Alinia has no significant drug interactions, and no warnings, alcohol interaction, contraindications, or neuropathies. However, regarding drug interactions, according to the PI, "Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur (e.g., **warfarin**)" (emphasis added). The sales aid fails to include this important information. This is especially concerning given that the table does reveal a warfarin interaction for Flagyl, and thus very strongly suggests that there is no risk of an interaction between warfarin and Alinia, when this isn't the case. Additionally, the sales aid omits other important risk information from the PI, including that ". . . nitazoxanide must be administered with caution to patients with hepatic and biliary disease, to patients with renal disease and to patients with combined renal and hepatic disease."

The overall effect of this presentation minimizes the risks associated with Alinia and misleadingly suggests that Alinia is safer than has been demonstrated.

Oral Statements

Furthermore, at the ICAAC/IDSA conference, your sales representatives claimed that there is no drug-drug interaction between Alinia and warfarin. This statement directly contradicts the PI and minimizes this risk associated with Alinia.

Unsubstantiated Compliance Claim

Sales Aid

The sales aid is misleading because it claims that Alinia is associated with a "99% compliance rate in clinical trials," when this is not supported by substantial evidence or substantial clinical experience. We are not aware of evidence to support this claim. If you have data to support this claim, please submit them to FDA for review.

Failure to Submit Under Form FDA-2253

FDA regulations require companies to submit specimens of any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use) and is required to include a copy of the product's current professional labeling. A copy of the sales aid referred to in this letter was not submitted to FDA under cover of Form FDA-2253 as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the sales aid and oral statements misbrand Alinia in violation of the Act, 21 U.S.C. 352(a); (f)(1); (n) & 321(n), and FDA implementing regulations. *See* 21 CFR 201.100(c)(1); 201.128; 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (ii). In addition, Romark failed to submit the sales aid to FDA under cover of Form FDA-2253, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Romark immediately cease the promotional activities and dissemination of violative promotional materials for Alinia such as those described above. Please submit a written response to this letter on or before June 9, 2009, stating whether you intend to comply with this request, listing all promotional activities and/or promotional materials (with the 2253 submission date) in use for Alinia as of the date of this letter, identifying which of these activities and/or materials contain violations such as those described above, and explaining your plan for discontinuing use of such promotional activities and/or violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional information. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #17360 in addition to the NDA numbers. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional activities and materials for Alinia comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

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